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Published in:
Journal of Rehabilitation Medicine

DOI (link to publication from Publisher):
10.2340/JRM.V54.241

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

ORIGINAL REPORT

PAIN TOLERANCE IN CHRONIC PAIN PATIENTS SEEMS TO BE MORE ASSOCIATED WITH PHYSICAL ACTIVITY THAN WITH DEPRESSION AND ANXIETY

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Objective: **To explore the associations between habitual self-reported physical activity, pain sensitivity and patient-reported outcomes (including pain intensity) in patients with chronic pain.**
Design: **Cross-sectional, experimental study.**
Subjects: **Patients ($n = 78$), age range 18–65 years, with different chronic pain conditions (> 3 months) were compared with age- and sex-matched healthy controls ($n = 98$).**
Methods: **Multivariate correlations between self-reported physical activity, pressure pain sensitivity, and patient-reported outcome measures were assessed.**
Results: **Lower perceived health status ($p < 0.001$, Cohen's d = 2.34), higher levels of depression ($p < 0.001$, Cohen's d = 1.77), and lower pain tolerance threshold ($p < 0.001$, Cohen's d = 1.66) were the most prominent variables discriminating patients from controls. In patients, bivariate and multivariate analyses showed that higher pressure pain tolerance was associated with male sex, lower pain intensity and fewer painful regions, higher self-efficacy and more self-reported physical activity, but not with lower levels of anxiety and depression.**
Conclusion: **Pain tolerance thresholds, as well as degree of depression and perceived health status discriminated between patients and controls, and there was an association between pain tolerance thresholds and level of self-reported physical activity in patients. This study highlights the importance of further research into how increased physical activity may improve pain sensitivity in patients with chronic pain.**

Key words: cuff pressure pain sensitivity; pain assessment; patient-reported outcome measures; physical activity.

Accepted Feb 22, 2022; Epub ahead of print Mar 11, 2022

J Rehabil Med 2022; 54: jrm00286

DOI: 10.2340/jrm.v54.241

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LAY ABSTRACT

Patients with chronic pain and healthy controls were included in this study of the relationships between self-reported physical activity, measurements of sensitivity to pressure pain, and questionnaire data. Pressure pain sensitivity was one of the most important factors discriminating between patients and controls, and there was a significant correlation between pain tolerance threshold and level of self-reported physical activity in patients (i.e. the lower pain thresholds the less physical activity). These results are relevant, as there are only a few previous studies examining the relationship between physical activity in patients with chronic pain and their sensitivity to pressure pain. More research is needed to explore how daily physical activity may improve chronic pain by, for example, increasing patient's tolerance to pain.

Physical inactivity and lifestyle changes are of significant health concern worldwide. Global estimates of physical inactivity indicate that 27.5% of adults and 81% of adolescents do not meet World Health Organization (WHO) recommendations (1). Physical inactivity is a recognized risk factor for many conditions, including cardiovascular disease, diabetes, cancer, dementia and depression (2), as well as chronic pain (3, 4). There are important evidence gaps regarding physical activity (PA) for people with chronic disease (1). PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure, and exercise is a subset of PA characterized by planned, structured, and repetitive PA (5).

Chronic pain with moderate to severe pain intensity affects approximately 20% of the general population (6). PA reduces the risk of chronic pain (7), and prescribed exercise significantly relieves symptoms in most pain conditions (8). Regarding psychological well-being as a result of PA, an overview of Cochrane Reviews (7) found that only 5 of 21 reviews included psychological well-being as an outcome measure (i.e. mental health, anxiety and depression). Both positive and no effects of

exercise on psychological health were reported. There is also evidence of prescribing exercise for managing many diseases (e.g. metabolic syndrome related disorders, heart and pulmonary diseases, muscle, bone and joint diseases, cancer, depression, asthma and type 1 diabetes) (9).

A single bout of aerobic exercise may lead to exercise-induced hypoalgesia (EIH) in healthy controls (10), but for patients with chronic pain it may, on the contrary, be less efficient or increase pain sensitivity (8). A more enduring hypoalgesia has been suggested as a feature associated with increased levels of habitual PA for healthy people (11). Lower sensitivity to experimental pressure pain is significantly associated with male sex and more habitual self-reported PA (11–14). Habitual PA and aerobic training may generally influence pain perception (11, 15, 16). Reduced pain sensitivity and decreased pain reports have been found during and after different types of exercise (17, 18). However, most studies have been performed on small samples of healthy males. A dose–response relationship was found between self-reported PA (but not when PA was measured with an accelerometer) and pain sensitivity, both in patients with chronic pain and in controls (11). Habitual PA was more strongly associated with pain tolerance in men than women (11).

Computerized cuff pressure algometry is a tool for assessment of pressure-pain sensitivity and mechanisms related to central modulation of pain, such as temporal summation and descending pain modulation (19). Cuff algometry mainly assesses sensitivity in deep somatic tissue and is less biased by inter- and intra-examiner variability than conventional handheld pressure algometry, messuring pressure pain thresholds (PPT) (13). Previously, cuff algometry studies found increased pressure pain sensitivity in fibromyalgia (20), whiplash-associated disorder (21), lateral epicondylalgia (22), and chronic pain after revision knee arthroplasty (19).

Previous research has indicated that psychological factors are associated with pain sensitivity (14, 23, 24). Depression is associated with higher pain sensitivity and greater pain, whereas self-efficacy is associated with lower pressure pain sensitivity (23). Symptoms of anxiety, depression and/or catastrophizing are associated with increased pain sensitivity (14, 24). We have previously shown that the cuff algometry assessed pain detection level (i.e. the pain threshold) is associated with both sex and PA levels in non-athletic healthy subjects (12), but there is a lack of knowledge about the correlations between pain sensitivity, PA, and psychological factors in patients with chronic pain.

The aim of this study was to explore the multivariate associations between habitual self-reported PA, pain sensitivity, and patient-reported outcomes (including pain intensity) in patients with chronic pain, first by comparing them with healthy controls and then by an in-depth analysis of patient data.

METHODS

Protocol

Demographic data and patient-reported outcome measures (PROMS) were collected from both patients and healthy controls. The dominant "writing hand" side was chosen for all assessments. All assessments were made in a single session. Cuff algometry with first single- and then double-chamber cuffs was completed on the arm and then on the leg. All assessments were repeated twice at each site, and the mean was calculated for further analyses. A short (<5 min) break was allowed when switching the cuff from arm to leg.

Participants

The patients with chronic pain included in the study underwent an interdisciplinary pain rehabilitation programme (IPRP) at the Pain and Rehabilitation Centre, University Hospital, Linköping, Sweden. Consecutive inclusion was used, and screening failures (i.e. evaluated for participation but not included) and/or dropouts were not registered. In total, 78 patients with different International Classification of Diseases 10th Revision (ICD-10)-coded chronic pain conditions (>3 months) were included.

Medical assessments and decisions to offer IPRP were performed by senior physicians, primarily specialists in rehabilitation medicine, or by physicians in training under the supervision of a senior colleague. The following inclusion criteria for IPRP were used: disabling chronic pain (on sick leave or experiencing major interference in daily life due to chronic pain); age between 18 and 65 years; no further medical investigations needed. General exclusion criteria from IPRP included severe psychiatric morbidity, abuse of alcohol and/or drugs, diseases that did not allow physical exercise, or presence of clinical indicators of a possible serious underlying condition. Additional specific exclusion criteria for this study were: compartment syndrome; neuropathic pain with allodynia; mental illness (investigator's judgment); pregnancy; language difficulties; pain duration shorter than 3 months; medication with strong opioids and anticoagulant treatment.

This is the third study using data from a cohort of healthy individuals (12, 25). The 98 controls were recruited through advertisement in a local newspaper. Inclusion criteria were: age between 20 and 65 years, and pain-free. A brief medical history was taken that excluded any current or previous presence of a pain condition.

The study was conducted in accordance with the Declaration of Helsinki. The study was granted ethical clearance by Linköping University Ethics Committee (2011/102-31). All participants were given written information about the study and consented to participate.

Detailed procedures

Demographic data. Age and sex were noted. Weight and height were recorded and body mass index (BMI) (in kg/m^2) calculated.

International Classification of Diseases 10th Revision (ICD-10). For patients, the ICD-10 code for the main diagnosis was noted.

Cuff pressure algometry. The experimental setup comprised a double-chamber 13-cm wide tourniquet cuff (a silicone high-pressure cuff, separated lengthwise into 2 equal-size chambers; VBM Medizintechnik GmbH, Sulz, Germany), a computer-controlled air compressor, and an electronic visual analogue scale (NociTech and Aalborg University, Denmark). The compression rate of the compressor was 1 kPa/s and was controlled by the computer. The cuff was connected to the compressor and wrapped around the mid-portion of the triceps surae muscles of the leg or around the heads of the biceps and triceps muscles of the arm. The maximum pressure limit was 100 kPa (760 mmHg). The stimulation could be aborted at any time by the subject, using a push button, or by the experimenter, via the computer or the pressure-release button.

During cuff pressure stimulation the pain intensity was simultaneously recorded using a 10-cm electronic visual analogue scale (VAS) and sampled 10 times/s. The subject adjusted the VAS score using a variable lever, and the magnitude was displayed on a red-light bar that was fully visible to the subject. Zero and 10-cm extremes on the VAS were defined as "no pain" and as "worst possible pain", respectively. Pain detection threshold (PDT; kPa), pain tolerance threshold (PTT; kPa), and pain tolerance pain intensity (PTI; cm) were extracted. PDT was defined as the pressure equivalent to the moment of transition from strong to painful pressure (i.e. VAS > 0.1cm for the first time). PTT was defined as the pressure level where the subject felt a pain sensation strong enough to feel like interrupting or stopping the session and did so by pressing the stop button (26). PTI was defined as the pain VAS score corresponding to PTT.

The degree of spatial summation (SR) was investigated calculating a summation ratio for PTT (the pressure measured with single cuff inflation was divided by the corresponding values using double cuff inflation). If PTT for double cuff (larger area that is stimulated) is lower than for single cuff, it shows spatial pain summation. The theoretical background to the term spatial is that there is an additive effect when simultaneously activating several synapses.

Patient-reported and healthy control-reported outcome measures (PROMs)

Godin Leisure-Time Exercise Questionnaire. The GLTEQ was used to estimate the habitual PA level (27, 28); it contains 2 questions. In the first question the person states how many times weekly they are performing "strenuous", "moderate" and "mild" exercise, respectively. The different intensities are described with examples in the questionnaire. A total leisure activity score was calculated by the times per week stated for the different intensities multiplied with 9 for strenuous, 5 for moderate, and 3 for mild. A high score indicates higher intensity and higher frequency of weekly leisure-time activities. The answers from the second question are used to calculate the frequency of weekly leisure-time activities pursued "long enough to work up a sweat". Only the first question is used in this study.

Pain characteristics (not assessed in healthy controls). Pain intensity before assessment (11-graded numerical rating scale; with endpoints: 0 = no pain and 10 = worst possible pain). Patients also denoted the anatomical extent of pain on a pain drawing encompassing 36 anatomical regions; the number of painful regions was thereby registered (painful regions; range: 0–36). Pain duration in months was also reported by the patients.

Hospital Anxiety and Depression Scale. HADS assesses anxiety and depression in 2 subscales of 7 item each (HADS-A and HADS-D) (29). A subscale score of 0–7 is a non-case, 8–10 is a doubtful case, and 11–21 indicates a case. Hence, high subscale scores indicate high levels of depression or anxiety.

European Quality of Life instrument. The EQ-5D captures a person's perceived health status. Only the second part of this instrument, EQ-VAS, has been used. The patient marks their self-perceived health on a 100-point scale, a "thermometer", with defined endpoints, on which high values indicate good health and low values poor health (30).

Anxiety Sensitivity Index. ASI is a 16-item measure tapping the fear of anxiety sensations. Subjects are asked to rate each response from almost not at all (0) to very much (4). The scores for the 16 questions are summed up to a total result from 0 to 64. High scores indicate high levels of anxiety. Studies have shown that the instrument has good psychometric properties (31).

General Self-Efficacy Scale. GSES contains 10 questions that evaluate the perception of confidence

in one's own ability. The questionnaire has been used in many contexts and has been tested for validity and reliability. The questions are answered according to a 4-point scale from "do not agree at all with" to "completely agree with". The sum of the points is between 10 and 40, where a higher sum represents a better outcome (32).

Quality of Life Scale. QOLS-S is composed of 16 items that, together, describe the quality-of-life concept, as follows: (1) Material comforts: home, food, modern conveniences, financial security; (2) Health: being physically fit and vigorous; (3) Relationships with parents, sibling and other relatives: communicating, visiting, helping; (4) Having and rearing children; (5) Close relationships with spouse or significant others; (6) Close friends; (7) Helping and encouraging others, participating in organizations, volunteering; (8) Participating in political organizations or public affairs; (9) Learning: attending school, improving knowledge; (10) Understanding yourself: knowing what life is about; (11) Work: job or home; (12) Expressing yourself creatively; (13) Socializing: meeting other people, doing things; (14) Reading, music or watching entertainment; (15) Participating in active recreation; and (16) Independence, being able to do things for yourself. A 7-point satisfaction scale is used. Participants estimate their satisfaction with their current situation, with a higher total score showing a higher satisfaction. The item scores are added to a total score, ranging from 16 to 112 (33).

Statistical analysis

IBM Statistical Package for the Social Sciences (SPSS, IBM Corporation, Somers, NY, USA) version 27.0 was used. $p \leq 0.05$ was considered statistically significant in all tests, with no adjustment for multiple comparisons. Unless stated otherwise, data are presented in the text as median (interquartile range; IQR). To compare groups, Mann–Whitney *U* test and Pearson χ^2 were used. Spearman's rho was used for bivariate correlations. Effect size was calculated as Cohen's d. Cohen's d of 0.20–0.49 is considered a small effect size, 0.50–0.79 medium effect size, and ≥0.80 large effect size (34). For multivariate data analysis by projection (MVDA), SIMCA-P+ (version 15, Umetrics AB, Umeå, Sweden) was used. Principal component analysis (PCA) and orthogonal projections to latent structures – discriminant analysis (OPLS-DA) were used, as well as OPLS. Briefly, PCA is an unsupervised technique that models the correlation structure of a dataset, and thereby enables identification of multivariate outliers and identification of prominent subgroups. OPLS-DA, which is a supervised technique, was used for group comparisons, enabling the identification of the X-variables (i.e. predictors) most responsible for group discrimination while at the same time taking the whole correlation structure of the material into consideration. X-variables with absolute values of $p(\text{corr}) > 0.4$ were considered "significant". $p(\text{corr})$ are the new variable values visualized in the loading plot, scaled as a correlation coefficient (ranging from –1.0 to +1.0) between model and original data. For each OPLS model, R^2 describes the goodness of fit and Q^2 describes goodness of prediction. Cross-validated analysis of variance (CV-ANOVA) with a $p \leq 0.05$ was used to validate the obtained model. Detailed information on the MVDA methodology has been published elsewhere (35, 36).

RESULTS

Group differences

Univariate statistics. ICD-10 diagnoses are shown in Table I, the 4 most frequent diagnoses being "musculoskeletal" (low back pain, cervicobrachial syndrome, fibromyalgia and myalgia) and together encompassing 50% of the patients. There were differences between patients and controls in age, BMI, cuff algometry variables, PA (GLTEQ) and other PROMs (Table II). There was no significant difference between the groups with respect to sex (Table II). The effect sizes by Cohen's d were large, with the largest for perceived health status (EQVAS), depression (HADS-D) and pain tolerance threshold (PTT arm): 2.34, 1.77 and 1.66, respectively (Table II).

Multivariate regression of group belonging. A PCA was performed on all subjects together and did not reveal any multivariate outliers ($n = 176$, 18 X-variables, 2 principal components, $R^2 = 0.47$, $Q^2 = 0.32$). All variables in Table II, except pain characteristics (pain intensity, pain regions, and pain duration), were included in an OPLS-DA using group belonging (patients vs controls) as dependent variable. As expected, given the results presented here, clear group separation was achieved (Fig. 1) and the model was highly significant (Table III). The 3 most important variables for group discrimination were perceived health status (EQVAS: $p(\text{corr}) = -0.86$, i.e. lower in patients), depression (HADS-D: $p(\text{corr}) = 0.83$, i.e. higher in patients), and pain tolerance (PTT arm: $p(\text{corr}) = -0.76$, and PTT leg: $p(\text{corr}) = -0.74$, both lower in patients) (Table III). Although there were differences in age and BMI between the groups (Table III), they were unimportant compared with the aforementioned 4 variables.

Table I. Diagnoses according to International Classification of Diseases 10th Revision (ICD-10**)

ICD-10	Patients (%)
M54.5 Low back pain	15.4
M53.1 Cervicobrachial syndrome	12.8
M79.7 Fibromyalgia	11.5
M79.1 Myalgia	10.3
R52.2* Other chronic pain (nociceptive)	7.7
R52.2* Other chronic pain (without known cause)	6.4
R52.9 Pain, unspecified	6.4
R53.0 Cervicocranial syndrome	5.1
R54.6 Pain in thoracic spine	3.8
M54.2 Cervicalgia	2.6
M54.4 Lumbago with sciatica	2.6
R52.2* Other chronic pain (neuropathic)	2.6
M43.1 Spondylolisthesis	1.3
M54.6 Pain in thoracic spine	1.3
M54.9 Dorsalgia, unspecified	1.3
M77.1 Lateral epicondylitis	1.3
M77.9 Enthesopathy, unspecified	1.3
M79.6 Pain in limb	1.3
Q79.6 Ehlers-Danlos syndrome	1.3
Q87.4 Marfan's syndrome	1.3
R52.1 Chronic intractable pain	1.3
T91.8 Sequelae of other specified injuries of neck and trunk	1.3

*In the Swedish version of ICD-10 there is a further subdivision of R52.2 into nociceptive, neuropathic and without known cause.

**Patients were not coded according to the new ICD-11 version, but all patients would have been classified within the new ICD-11 chronic pain diagnosis (MG30), which is subdivided into 7 subsections.

In-depth analyses of patient data

Multivariate regression of PTT arm. As one of the most important variables discriminating between patients and controls was pain tolerance threshold (PTTarm) (Table III), in the next step this variable (Y-variable) in the patients ($n=77$) was regressed using demographic data and PROMs (including the 3 pain variables) listed in Table II as regressors (X-variables). This was done in order to better understand the influence of these variables on pain tolerance. The most important regressors for higher PTTarm were male sex, pain intensity and the number of painful regions, followed by self-efficacy (GSES) and self-reported PA (GLTEQ) (Table IV).

Bivariate correlations. The results from the OPLS model in Table IV were confirmed by bivariate correlations: PTTarm and pain intensity correlated negatively (rho = –0.38, $p=0.001$), as did PTTarm and number of painful regions (rho = –0.29 and $p=0.011$). PTTarm and self-efficacy (GSES) correlated positively (rho = 0.30 and $p=0.008$), as did PTTarm and PA (GLTEQ) (rho = 0.23, $p=0.047$). Moreover, male patients had higher PTTarm values than female patients (76 (54–96) kPa vs 37 (27–50) kPa, $p<0.001$). No significant correlation between PTTarm and anxiety, depression or the other variables was found.

Multivariate regression of PTT arm and PTT leg together. Appendices SI and SII report the effect of adding PTTleg as an additional Y-variable (i.e. these models are multi-Y models), both when using the same X-variables, as in Table IV, and when adding more X-variables only available in patients, respectively. In all models, sex, pain intensity and self-efficacy measures remained the strongest predictors of PTTarm (taking PTTleg into consideration), followed by PA and BMI, which were equally important (although

Table II. Overview of study data, patients with chronic pain vs healthy controls

Variables	Controls ($n=98$)	Patients ($n=78$)	Statistics (p-value)	Effect sizeby Cohen's d
Demographic data				
Age, years	30 (26–44)	43 (35–50)	<0.001	0.69
Sex (% females)	51	61.5	0.16	N.A.
BMI, kg/m^2	23.8 (22–25.5)	24.9 (23.5–32.5)	0.002	0.56
Cuff algometry data				
PDT arm, kPa	22.9 (12.2–34.4)	10.4 (7.6–16.9)	<0.001	0.87
PDT leg, kPa	18.3 (11.5–35.4)	8.6 (6.8–12.6)	<0.001	0.92
PTT arm, kPa	100.0 (89.4–100)	48.8 (33.8–76.7)	<0.001	1.66
PTT leg, kPa	100.0 (68–100)	38.2 (25.5–61.3)	<0.001	1.57
PTI arm, cm (0–10)	6.2 (3.4–9.2)	9.5 (7.7–10)	<0.001	0.99
PTI leg, cm (0–10)	8.3 (5.1–10)	10.0 (8–10)	0.001	0.58
SR arm	1 (1–1)	1.2 (1.1–1.3)	<0.001	0.29
SR leg	1.2 (1–1.4)	1.3 (1.1–1.6)	0.018	0.24
Patient-reported outcome measures (PROMs)				
Pain intensity (0–10)	N.A.	6 (5–7)	N.A	N.A
Painful regions (0–36)	N.A.	13 (7–18)	N.A.	N.A.
Pain duration, months	N.A.	33.5 (24–120)	N.A.	N.A.
GLTEQ	45.5 (28.8–63.5)	31 (19.5–49)	0.001	0.5
QOLS	92 (84–98)	74.5 (61–84)	<0.001	1.35
GSES	32 (28.8–35)	27 (23.5–31)	<0.001	0.87
HADS-A	3 (1–5)	7 (4–10.5)	<0.001	1.12
HADS-D	1 (0–3)	7 (4–10)	<0.001	1.77
ASI	8 (6–12)	17 (10–26)	<0.001	0.8
EQVAS	90 (80–95)	50 (33.5–65)	<0.001	2.34

Data are expressed as median (25th–75th percentiles), except for sex. Results from single chamber cuff are presented for PDT, PTT and PTI.

ASI: Anxiety Sensitivity Index; EQ-VAS: second part of the European Quality of Life instrument, which captures a person's perceived health status; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS-A and HADS-D: Anxiety and Depression subscale of Hospital Anxiety and Depression Scale; PDT: pain detection threshold; PTI: pain tolerance pain intensity; PTT: pain tolerance threshold; QOLS: Quality Of Life Scale; GSES: General Self-Efficacy Scale; SR: spatial summation ratio.

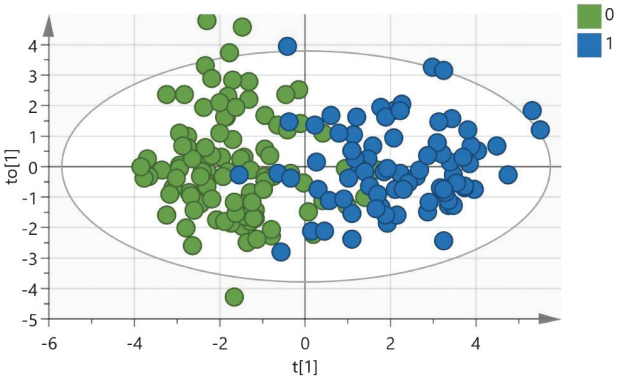

Fig. 1. Score plot of the orthogonal partial least squares – discriminant analysis (OPLS-DA) model, illustrating group separation between patients (1, *blue dots*) and controls (0, *green dots*). The 2 axes represent the 2 latent variables of the model. Class separation between patients and controls occurs along the t[1] axis (inter-class variation), whereas the to[1] axis represents intra-class variation.

Table III. Variable importance for group discrimination (patients vs controls) in descending order of absolute *p*(corr) values, in orthogonal partial least squares – discriminant analysis (OPLS-DA) model

Variables	*p*(corr)
EQVAS	−0.86
HADS-D	0.83
PTT arm	−0.76
PTT leg	−0.74
QOLS	−0.73
HADS-A	0.60
PDT leg	−0.54
GSES	−0.53
PDT arm	−0.48
ASI	0.47
PTI arm	0.42
Age	0.41
BMI	0.40
GLTEQ	−0.36
SR arm	0.34
PTI leg	0.27
Sex	−0.07
SR leg	0.06
n	176
R2	0.69
Q2	0.66
CV-ANOVA *p*-value	< 0.001

p(corr) > 0.4 was considered significant; for an explanation of *p*(corr), see the Statistics section. Positive *p*(corr) values signify higher levels in patients than in controls, and vice versa. Results from single chamber cuff are presented regarding PDT, PTT and PTI.

ASI: Anxiety Sensitivity Index; EQ-VAS: the second part of the European Quality of Life instrument and captures a person's perceived health status; GLTEQ: Godin Leisure-Time Exercise Questionnaire; HADS-A and HADS-D: Anxiety and Depression subscale of Hospital Anxiety and Depression scale; PDT: pain detection threshold; PTI: pain tolerance pain intensity; PTT: pain tolerance threshold; QOLS: Quality Of Life Scale; GSES: General Self-Efficacy Scale; SR: spatial summation. The 4 bottom rows are: *n*, R^2 = goodness of fit, Q2 = goodness of prediction, and CV-ANOVA *p*-value = *p*-value for the cross-validated analysis of variance (CV-ANOVA).

the direction of the association differed, BMI being negatively correlated with PTTarm). Also, the Pain Catastrophizing Scale (PCS) was important, being negatively correlated with PTTarm. The bivariate correlation between PTTarm and PTTleg was strong (rho = 0.79, $p > 0.001$).

DISCUSSION

This study showed that high pain tolerance threshold (PTTarm) in patients with chronic pain was significantly associated primarily with male sex, low pain intensity, low number of painful regions, high self-reported PA, and high self-efficacy, but not with low anxiety and depression. The discussion focuses on the most novel findings, which are those about PA and pain sensitivity.

Pain sensitivity and physical activity

Martinez-Calderon et al. have shown that pain tolerance in patients is associated with psychological factors (23). However, the current results show that, in patients, depression (and perhaps to a lesser degree anxiety) is a weaker regressor of pain tolerance than PA. The findings of the current study about the relative unimportance of psychological factors, at least concerning depression, in this respect are congruent with Jensen et al. (37), who, in patients with fibromyalgia, found that depression, anxiety, and catastrophizing did not correlate with ratings of clinical experimental pain (using a computer-controlled pressure stimulator) and did not modulate brain activity during experimental pain.

The current data on the relationship between pain tolerance and self-reported PA among patients with chronic pain are in line with the minimal previous research available on this subject, Årnes et al. showing a dose–response relationship between self-reported PA and pain sensitivity in patients with chronic pain (11).

In our previous study on healthy subjects, PDT was associated with both sex and self-reported PA level (12). In the current study, PTT had a stronger weight than PDT in discriminating between patients and controls (although PDT was also of some importance, see Table III). The current data also confirm that sex is the strongest predictor for PTT. It was also shown that BMI and PCS were negatively correlated with PTT in line with a previous study (24).

Self-reported physical activity or accelerometer?

It has been claimed that measuring PA with a questionnaire, such as GLTEQ, is not as reliable as, for example, accelerometers (38). Accelerometry is a feasible large-scale alternative to energy expenditure estimation as a gold standard (39). However, Årnes et al. found that, although higher self-reported habitual PA was connected with higher experimental pain tolerance in a population-based sample, especially for men, this was *not* the case when assessing PA with accelerometry (11). One can speculate that, although accelerometers may be suitable for measuring PA time and intensity,

Table IV. Variable importance for regression of pain tolerance threshold (PTT) arm for patients in descending order of absolute *p*(corr) values in orthogonal partial least squares (OPLS) model

Variables	*p*(corr)
Sex*	0.79
Pain intensity	−0.58
Painful regions	−0.50
GSES	0.35
GLTEQ	0.29
Pain duration	−0.28
ASI	−0.25
BMI	−0.22
HADS-A	−0.22
EQVAS	0.13
Age	0.09
QOLS	0.06
HADS-D	−0.06
n	77
R2	0.46
Q2	0.28
CV-ANOVA *p*-value	< 0.001

*Male sex is associated with higher PTT.

p(corr) > 0.4 was considered significant; for an explanation of *p*(corr), see the Statistics section. A positive *p*(corr) signifies a positive correlation with PTT arm.

ASI: Anxiety Sensitivity Index, EQ-VAS: second part of the European Quality of Life instrument, which captures a person's perceived health status; GLTEQ: Godin Leisure-Time Exercise Questionnaire; GSES: General Self-Efficacy Scale; HADS-A and HADS-D: Anxiety and Depression subscale of Hospital Anxiety and Depression scale; QOLS: Quality Of Life Scale. The 4 bottom rows are: *n*, R^2 = goodness of fit, Q^2 = goodness of prediction, and CV-ANOVA *p*-value = *p*-value for the cross-validated analysis of variance (CV-ANOVA).

perhaps questionnaires are more useful for ranking and comparing the relative activity levels of participants. Further studies on the association between PA and pain tolerance should assess both accelerometer and self-reported questionnaires.

Clinical implications

A single bout of aerobic exercise may induce exercise-induced hypoalgesia in healthy controls, while the opposite may be seen in patients (8); however pressure pain sensitivity were found to increase (hypoalgesia) after an exercise intervention lasting 4-6 months for patients with chronic pain (18). For patients, exercise-induced pain exacerbations may be a major barrier to initiation of activities and thereby lead to physical inactivity and further compromise comorbidities, such as cardiovascular disease, diabetes, cancer, dementia and depression (2). The possibility of modulating pain sensitivity by PA in patients with chronic pain should not be discarded, and it is important to study the complex relationships between pain sensitivity and PA.

Previous cuff algometry studies have demonstrated increased pressure pain sensitivity in fibromyalgia (20), whiplash-associated disorder (21) and other chronic pain conditions (19, 22). Cuff algometry has been shown to be a valuable method for pain sensitivity studies, and is automated, reproducible, and clinically applicable (13).

It is not known if patients with increased pressure pain sensitivity perform less PA because of their pain condition, or if they perform less PA because of other circumstances, and that this, in turn, influences their pain sensitivity. In order to examine that, one would need to follow a group of patients and study their pain sensitivity and PA over time and see how they relate to each other. Further research is necessary to examine if pain tolerance increases when patients are able to increase their PA after an intervention such as the IPRP. During such a programme the patient should receive help with graded exposure as well as education concerning the fact that an initial increase in pain sensitivity when they start increasing PA is not a sign of tissue damage. When integrated in a comprehensive pain neuroscience education programme, one can hypothesize that patients with impaired EIH may benefit from a decrease in their catastrophic thinking about potential exercise-induced symptom flares, increased acceptance about such flares, and improved confidence that these negative reactions will dissipate with time (8).

Study limitations

A limitation that hampers the generalizability of the study is that screening failures and dropouts were not registered prospectively (i.e. the possibility of a selection bias). Moreover, cross-sectional studies have obvious drawbacks, and longitudinal studies are warranted. The questionnaire assessment of PA has obvious limitations, as mentioned. Furthermore, the diagnoses reflect the group of patients in the IPRP, but the heterogeneity of diagnoses can also be viewed as a limitation. To be able to better interpret the results of a specific pain diagnosis, it would be favourable to only have patients with the same diagnosis. In addition, a deeper understanding of how PA affects pain sensitivity should include the use of different biomarkers, e.g. concerning the relationship between pain and chronic inflammation (40). Finally, although depression and anxiety were weaker regressors of pain tolerance than PA (see Table IV), it is unclear if the difference is meaningful from a clinical point of view. Statistically, there is a difference, and depression is not a stronger regressor, thus PA is at least as important as the level of mood disorder.

CONCLUSION

Pain tolerance threshold discriminated between patients with chronic pain and controls, and a significant correlation was found between pain tolerance threshold and level of self-reported PA in patients. This adds information to the few existing studies examining the relationship between the level of self-reported PA in patients with chronic pain and their pain sensitivity.

ACKNOWLEDGEMENTS

The authors thank Eva-Britt Lind and Ulrika Wentzel Olausson for their help and assistance with performing measurements and acquiring data.

The study was funded by ALF Research Grants Region Östergötland (EB), and a Research grant, Sinnescentrum, Region Östergötland (OS). The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121).

Olof Skogberg, Linn Karlsson, Björn Börsbo, Emmanuel Bäckryd and Dag Lemming have no conflicts of interest to declare. Björn Gerdle is currently (since 2020) involved in a collaboration with Pfizer Inc. concerning chronic low back pain and osteoarthritis. Thomas Graven-Nielsen and Lars Arendt-Nielsen have no conflicts of interest to declare in relation to the current study.

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